Online supplement (Extended Data Sheet) for Klein et al., Genetic Markers of ADHD-Related Variations in Intracranial Volume. Am J Psychiatry (doi: 10.1176/appi.ajp.2018.18020149)

SUPPLEMENTARY MATERIAL: **Extended data sheet for results of post hoc analyses for pallidum and thalamus**

Contents

Linkage disequilibrium score regression

Table 1. SNP heritability analyses for MRI brain volumes and genetic correlation with ADHD.

Brain region	N	Heritability	SE	Genetic correlation with ADHD	SE	Z	P
Pallidum	11,640	0.1557	0.0478	-0.04864	0.08893	-0.547	0.5844
Thalamus	11,694	0.095	0.0442	0.06506	0.1132	0.5747	0.5655

Heritability and genetic correlation were estimated by using free intercepts.

SNP effect concordance analysis

Table 2. Results of pleiotropy and concordance test of SNP Effect Concordance Analysis. Brain volume GWAS-MA was conditioned on ADHD GWAS-MA.

Brain volume	P pleiotropy	CI pleiotropy	P concordance	CI concordance	Direction of SNP effects
Pallidum	0.000999	5.12×10^{-5}-0.00564	1	0.996-1	/
Thalamus	0.00799	0.00406-0.0157	0.17	0.148-0.194	concordant

P-values and confidence intervals (CI) were obtained based on 1,000 permutations.
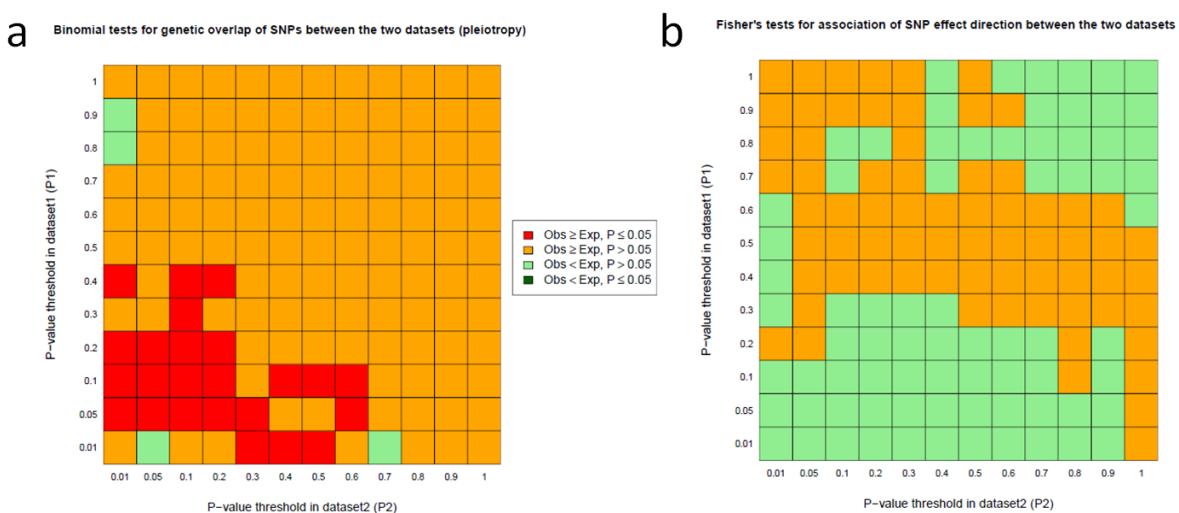
Figure 1: Global evidence of pleiotropy (**a**) and concordance (**b**) between ADHD GWAS and pallidum volume. P1 in the plot is the ADHD GWAS and P2 is the pallidum volume GWAS.
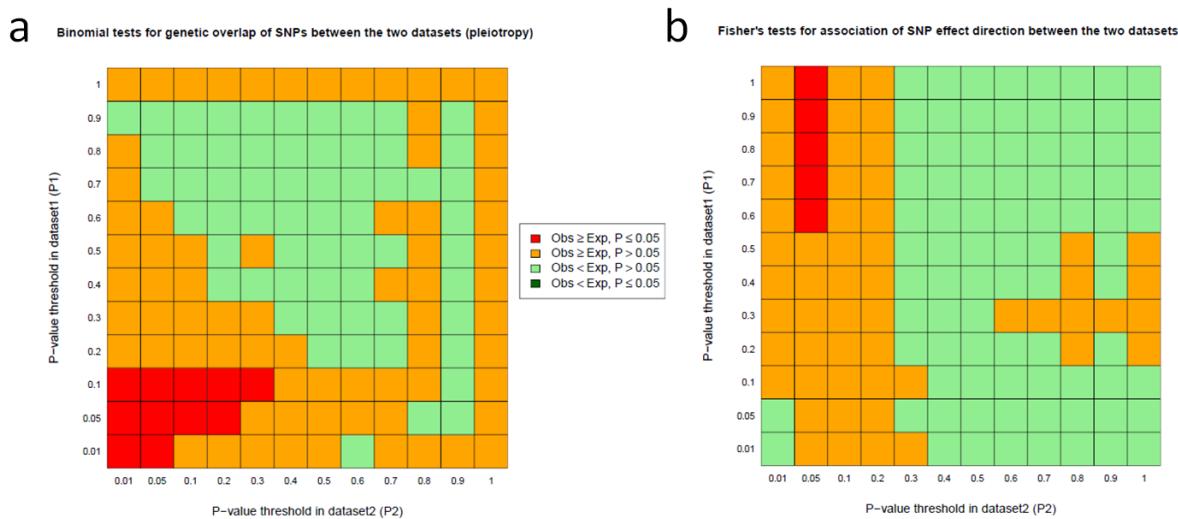
Figure 2: Global evidence of pleiotropy (**a**) and concordance (**b**) between ADHD GWAS and thalamus volume. P1 in the plot is the ADHD GWAS and P2 is the thalamus volume GWAS.

Sign tests

Table 3. Sign test results in brain volume cohorts.

P threshold	Brain region	N opposite direction	Proportion	P
< 5x10^{-8}	Pallidum	3	0.3	0.945
	Thalamus	3	0.3	0.945
< 1x10^{-6}	Pallidum	16	0.46	0.75
	Thalamus	14	0.4	0.912
< 1x10^{-5}	Pallidum	52	0.53	0.307
	Thalamus	43	0.44	0.906

Test of whether the proportion of index SNPs with estimated effects in the *opposite* direction as the ADHD GWAS-MA is greater than expected by chance. The expected proportion under the null hypothesis is 0.5. At threshold P<5x10^{-8} 4 index SNPs were not available in the brain volume GWAS-MA data, so were 9 at threshold P<5x10^{-6} and 34 at threshold P<5x10^{-5}.

Weighted SNP meta-analyses
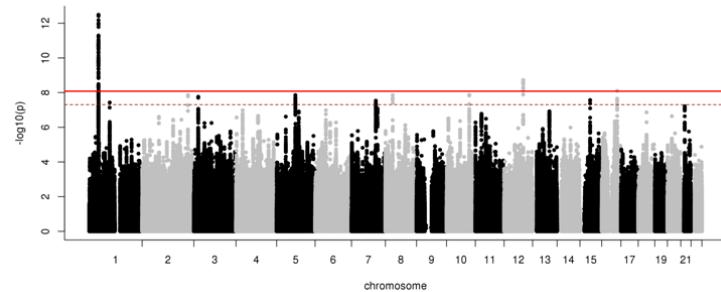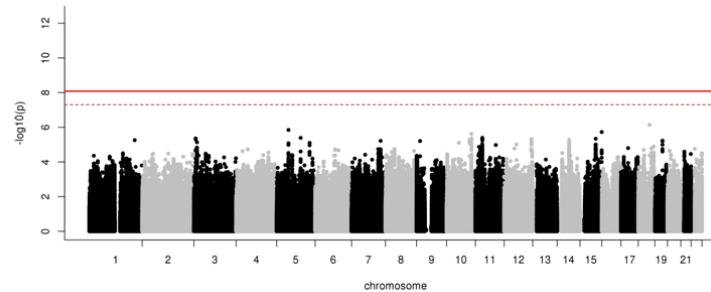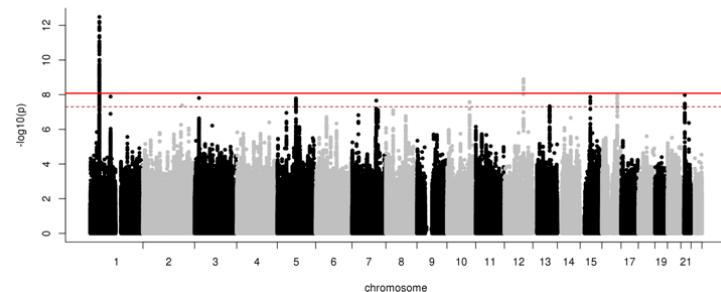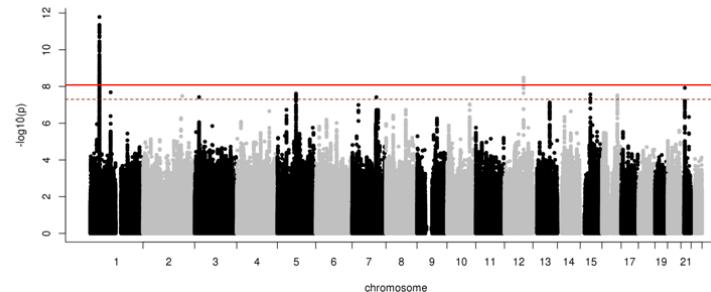
Figure 3: Common genetic variants associated with ADHD, pallidum volume and ADHD+pallidum volume. Shown here are Manhattan plots, in which every point represents a single genetic variant plotted according to its genomics position (x-axis) and its $-\log_{10}(P)$ for association with the respective trait (y-axis). The solid bright red line represents the study-wide genome-wide significance of $P<8.33\times10^{-9}$, and the dashed dark red line represents the genome-wide significance of $P<5\times10^{-8}$. (**a**) PGC+iPSYCH ADHD GWAS-MA. (**b**) ENIGMA pallidum volume GWAS-MA. (**c**) ADHD+pallidum volume weighted GWAS-MA. (**d**) ADHD+pallidum volume naive GWAS-MA.
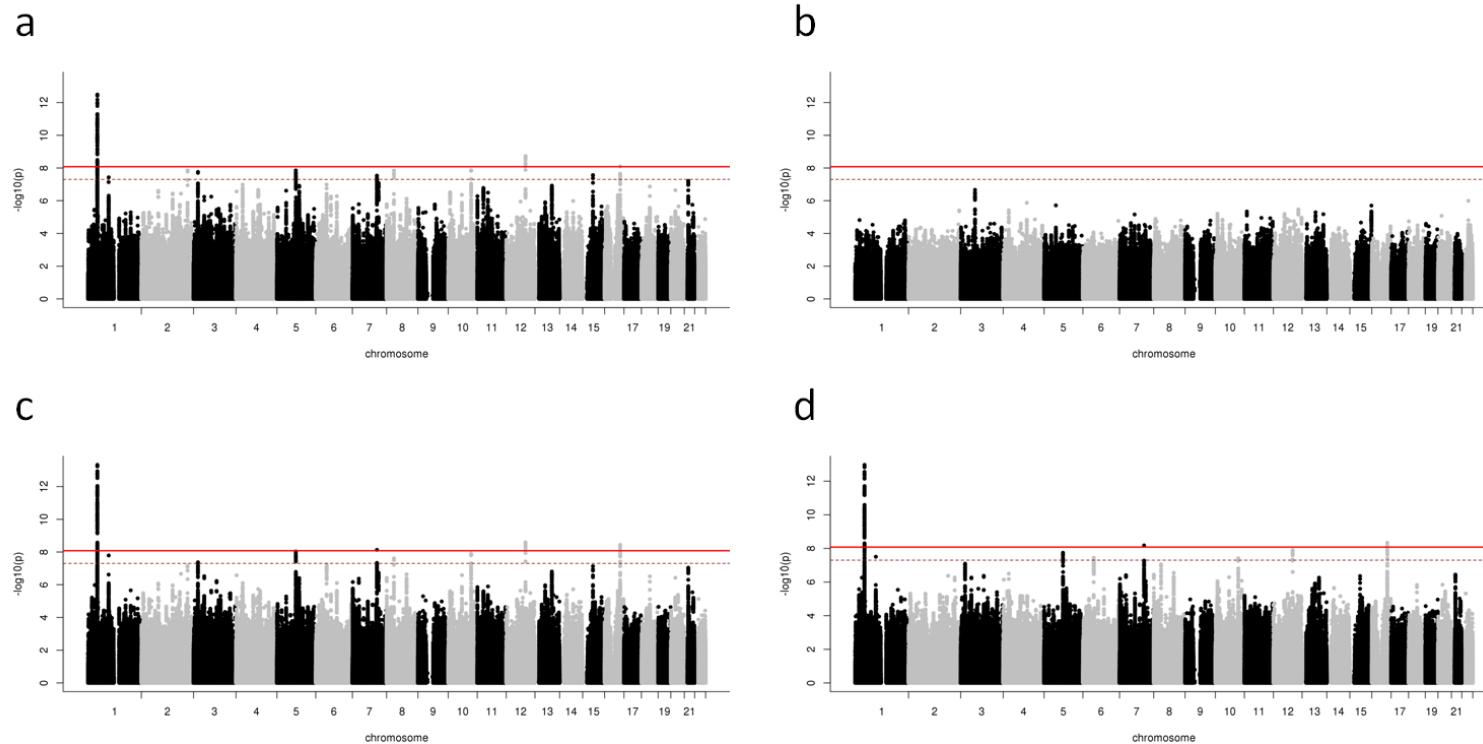
Figure 4: Common genetic variants associated with ADHD, thalamus volume and ADHD+thalamus volume. Shown here are Manhattan plots, in which every point represents a single genetic variant plotted according to its genomics position (x-axis) and its $-\log_{10}(P)$ for association with the respective trait (y-axis). The solid bright red line represents the study-wide genome-wide significance of $P<8.33\times10^{-9}$, and the dashed dark red line represents the genome-wide significance of $P<5\times10^{-8}$. (**a**) PGC+iPSYCH ADHD GWAS-MA. (**b**) ENIGMA thalamus volume GWAS-MA. (**c**) ADHD+thalamus volume weighted GWAS-MA. (**d**) ADHD+thalamus volume naive GWAS-MA.

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Gene-wide GWAS-MAs

Table 4: Results of MAGMA gene-based associations of all genes for ADHD and pallidum volume.

>>> see file *MAGMA_comparison_ADHD_pallidum.xlsx* <<<

Genome-wide gene-based results of MAGMA analysis. Entrez-ID (GENE), Chromosome (CHR), Start (START) and end (STOP) position of the genes, number of SNPs in the genes (N SNPs), effective number of SNPs included (NPARAM), the total sample size (N), test statistics (ZSTAT), and gene-based p-values for ADHD GWAS-MA (tab 1), ENIGMA pallidum GWAS-MA (tab 2), and the weighted ADHD+pallidum GWAS-MA (tab 3) are shown. Genes were considered gene-wide significant, if they reached the Bonferroni correction threshold adjusted for the total number of genes (N=18,306; $P<2.731 \times 10^{-6}$; genes marked in bold).

Table 5: Results of MAGMA gene-based associations of all genes for ADHD and thalamus volume.

>>> see file *MAGMA_comparison_ADHD_thalamus.xlsx* <<<

Genome-wide gene-based results of MAGMA analysis. Entrez-ID (GENE), Chromosome (CHR), Start (START) and end (STOP) position of the genes, number of SNPs in the genes (N SNPs), effective number of SNPs included (NPARAM), the total sample size (N), test statistics (ZSTAT), and gene-based p-values for ADHD GWAS-MA (tab 1), ENIGMA thalamus GWAS-MA (tab 2), and the weighted ADHD+ thalamus GWAS-MA (tab 3) are shown. Genes were considered gene-wide significant, if they reached the Bonferroni correction threshold adjusted for the total number of genes (N=18,306; $P<2.731 \times 10^{-6}$; genes marked in bold).

Table 6: Comparison of genome-wide significant MAGMA gene-based results for ADHD and pallidum.

Gene Name	EntrezID	P_{ADHD}	$P_{pallidum}$	$P_{ADHD+pallidum}$
ST3GAL3	6487	5.57E-13	0.33343	1.06E-13
PTPRF	5792	7.6E-13	0.52848	1.44E-12
SZT2	23334	3.95E-12	0.79288	8.83E-12
KDM4A	9682	1.77E-11	0.40584	1.72E-11
DUSP6	1848	1.47E-11	0.58627	3.5E-11
HYI	81888	2.71E-11	0.7758	6.88E-11
MEF2C	4208	1.63E-10	0.2715	6.93E-11
ELOVL1	64834	3.55E-10	0.74887	6.01E-10
CDC20	991	4.11E-10	0.72683	7.23E-10
MED8	112950	1.7E-09	0.84361	2.37E-09
MPL	4352	1.31E-09	0.61228	3.42E-09
ARTN	9048	4.73E-08	0.29146	8.26E-09
SEMA6D	80031	1.62E-09	0.78929	9.61E-09
IPO13	9670	7.42E-08	0.19523	1.9E-08
TIE1	7075	1.7E-08	0.42991	5.57E-08
SORCS3	22986	2.22E-08	0.66127	1.29E-07
FEZF1	389549	9.51E-08	0.59552	1.32E-07
DPH2	1802	3.14E-07	0.20882	1.46E-07
ATP6V0B	533	6.26E-07	0.23988	2.84E-07
C1ORF210	149466	1.81E-07	0.29154	4.44E-07
B4GALT2	8704	1.03E-06	0.24352	4.64E-07
FOXP2	93986	4.14E-08	0.73244	1.08E-06
POC1B	282809	1.43E-06	0.72788	1.56E-06
CDH8	1006	4.54E-08	0.9676	1.86E-06
TMEM125	128218	6.17E-07	0.2747	1.89E-06
TALDO1	6888	2.54E-06	0.41757	2.16E-06

Genome-wide significant gene-based results of MAGMA for the 26 genes overlapping between the ADHD and ADHD+pallidum data sets. No gene showed stronger association (smaller cross-trait p-value and nominally significant p-value ($P<0.05$) in pallidum data set) in the cross-trait meta-analysis compared to the separate analyses of ADHD and pallidum.

Table 7: Comparison of genome-wide significant MAGMA gene-based results for ADHD and thalamus.

Gene Name	EntrezID	P_{ADHD}	$P_{thalamus}$	$P_{ADHD+thalamus}$
ST3GAL3	6487	2.76E-14	0.68469	1.84E-13
PTPRF	5792	1.23E-13	0.44022	2.04E-13
SZT2	23334	1.26E-12	0.46816	1.67E-12
KDM4A	9682	4.07E-12	0.38912	4.99E-12
HYI	81888	3.28E-12	0.37782	9.74E-12
MEF2C	4208	5.99E-10	0.41413	1.73E-10
ELOVL1	64834	1.68E-10	0.53903	1.88E-10
CDC20	991	1.52E-10	0.55619	2.15E-10
DUSP6	1848	4.53E-11	0.48078	4.73E-10
MPL	4352	1.84E-09	0.50396	5.34E-10
MED8	112950	2.39E-10	0.53891	1.03E-09
SEMA6D	80031	3.48E-09	0.57583	3.3E-09
TIE1	7075	1.11E-08	0.62267	1.2E-08
FOXP2	93986	3.5E-07	0.027619	**1.62E-08**
SORCS3	22986	1.64E-08	0.48316	1.99E-08
ARTN	9048	5.38E-08	0.89288	4.42E-08
IPO13	9670	3.79E-08	0.88159	9.19E-08
C1ORF210	149466	1.97E-07	0.79855	1.37E-07
CDH8	1006	4.93E-08	0.60852	4.17E-07
DPH2	1802	1.02E-07	0.91256	4.95E-07
TMEM125	128218	5.82E-07	0.79847	5.41E-07
FEZF1	389549	6E-07	0.76437	7.13E-07
ATP6V0B	533	2.43E-07	0.91095	9.32E-07
B4GALT2	8704	4.38E-07	0.9218	1.45E-06
ADD1	118	1.24E-06	0.69817	1.88E-06
KIZ	55857	6.47E-07	0.70382	2E-06

Genome-wide significant gene-based results of MAGMA for the 26 genes overlapping between the ADHD and ADHD+thalamus data sets. One gene showed stronger association (smaller cross-trait p-value and nominally significant p-value (P<0.05, marked in bold) in thalamus data set) in the cross-trait meta-analysis compared to the separate analyses of ADHD and thalamus.

Reciprocal lookup of genome-wide significant associations

Table 8: Reciprocal look-up of significantly associated ADHD index SNPs in brain volume GWAS data

									Pallidum		Thalamus	
Index SNP	A1	A2	chr	pos	OR $_{ADHD}$	P$_{ADHD}$	Proxy	LD to index (r2)	Zscore	P	Zscore	P
rs11420276	G	GT	1	44184192	1.113	2.14×10^{-13}	rs112984125	0.976	-1.10924	0.2673	-1.53984	0.1236
rs1222063	A	G	1	96602440	1.101	3.07×10^{-8}	rs1222067	0.751	-0.25206	0.801	**0.066329**	0.9471
rs2391769	A	G	1	96978961	0.927	3.96×10^{-8}	/	/	**-1.44561**	0.1483	**-1.27605**	0.2019
rs9677504	A	G	2	215181889	1.124	1.39×10^{-8}	/	/	-2.12638	0.03347	-0.54654	0.5847
rs4858241	T	G	3	20669071	1.082	1.74×10^{-8}	/	/	-1.20436	0.2284	-0.40322	0.6868
rs28411770	T	C	4	31151456	1.09	1.15×10^{-8}	rs7674790	0.783	-1.80536	0.07101	-1.1548	0.2482
rs4916723	A	C	5	87854395	0.926	1.58×10^{-8}	/	/	**-0.70568**	0.4804	**-0.58023**	0.5618
rs304132	A	G	5	88215594	0.925	4.22×10^{-8}	/	/	**-0.21618**	0.8289	**-0.79279**	0.4279
rs5886709	G	GTC	7	114086133	1.079	1.66×10^{-8}	rs7795397	0.941	**0.465181**	0.6418	**0.601321**	0.5476
rs74760947	A	G	8	34352610	0.835	1.35×10^{-8}	/	/	0.287181	0.774	**-0.1583**	0.8742
rs11591402	A	T	10	106747354	0.911	1.34×10^{-8}	/	/	**-0.39996**	0.6892	**-0.66446**	0.5064
rs1427829	A	G	12	89760744	1.083	1.82×10^{-9}	/	/	**1.07631**	0.2818	**0.560579**	0.5751
rs281324	T	C	15	47754018	0.928	2.68×10^{-8}	/	/	**-1.21208**	0.2255	0.004724	0.9962
rs212178	A	G	16	72578131	0.891	7.68×10^{-9}	/	/	**-0.62581**	0.5314	**-1.25413**	0.2098

GWAS results from pallidum and thalamus brain volume GWASs for the genome-wide significant loci identified in the ADHD GWAS. Replication is tested for the index variant from the ADHD GWAS, or for a proxy variant when the index variant is not present in the brain volume cohorts. Effects (Z-score or odds ratio [OR] with reference to allele 1 [A1]) that are sign concordant with the ADHD GWAS are indicated in bold.